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## Research funded by grants

### Flame retardant Firemaster 550 confirmed as endocrine disruptor

An animal study conducted by NIEHS grantees shows that perinatal exposure to the flame retardant Firemaster 550, commonly found in house dust, is associated with endocrine disrupting effects. The findings reveal the need for more research on the mechanisms involved and the health effects of humans exposed to the product.

The researchers evaluated the effects of Firemaster 550 in rats and found that its components accumulated in tissues of exposed mice and their offspring. The offspring exhibited advanced female puberty, weight gain, male cardiac hypertrophy, and problems with exploratory behaviors. The results suggest that Firemaster 550 may affect growth and neurodevelopment.

*Citation:* Patisaul HB, Roberts SC, Mabrey N, McCaffrey KA, Gear RB, Braun J, Belcher SM, Stapleton HM.  
(<http://www.ncbi.nlm.nih.gov/pubmed/23139171>)

2013. Accumulation and endocrine disrupting effects of the flame retardant mixture Firemaster 550 in rats: an exploratory assessment. *J Biochem Mol Toxicol* 27(2):124-136. [\[Synopsis\]](#)

### **Tributyltin linked to transgenerational obesity**

An NIEHS-supported study showed that mice prenatally exposed to the endocrine disruptor tributyltin (TBT) were more likely to be obese, and the effects persisted in subsequent generations not directly exposed to TBT. The findings hold important implications for understanding obesity in people.

TBT is used as an antifungal agent in some paints, certain plastics, and consumer products. Researchers exposed pregnant mice to doses of TBT that were comparable to the established human tolerable daily intake. The offspring of the pregnant mice exposed to TBT, and the subsequent two generations of mice, had a greater number of fat cells, larger fat cells, and heavier fat depots. If TBT has similar effects on people, then exposure to it and other endocrine disruptors could reprogram the metabolism of exposed individuals as well as future generations, predisposing them to weight gain.

*Citation:* [Chamorro-Garcia R, Sahu M, Abbey RJ, Laude J, Pham N, Blumberg B.](#)  
(<http://www.ncbi.nlm.nih.gov/pubmed/23322813>)

2013. Transgenerational inheritance of increased fat depot size, stem cell reprogramming, and hepatic steatosis elicited by prenatal exposure to the obesogen tributyltin in mice. *Environ Health Perspect* 121(3):359-366. [\[Synopsis\]](#)

### **Reducing air pollution continues to increase life expectancy**

NIEHS grantees report that air pollution reductions occurring from 2000 to 2007 were associated with improved life expectancy. These results show that the last decade of air pollution control continues to positively affect public health.

From 2000 to 2007, U.S. levels of particulate matter less than 2.5 micrometers in diameter (PM<sub>2.5</sub>) have declined, but at a slower rate than between 1980 and 2000. To find out if these levels continued to improve life expectancy, the researchers looked at yearly average PM<sub>2.5</sub> and life expectancy data for 545 rural and urban U.S. counties, from 2000 to 2007. Controlling for socioeconomic status, smoking prevalence, and demographic characteristics, they found that the average life expectancy increased by 0.35 years for every 10 micrograms per meter decrease in PM<sub>2.5</sub> concentration. The association between life expectancy and air pollution levels was stronger in more urban and densely populated counties.

*Citation:* [Correia AW, Pope CA 3rd, Dockery DW, Wang Y, Ezzati M, Dominici F.](#)  
(<http://www.ncbi.nlm.nih.gov/pubmed/23211349>)

2013. Effect of air pollution control on life expectancy in the United States: an analysis of 545 U.S. counties for the period from 2000 to 2007. *Epidemiology* 24(1):23-31. [\[Synopsis\]](#)

### **Early pregnancy inflammation could increase autism risk**

Inflammation during pregnancy could be associated with an increased risk for autism, according to research that was partially funded by NIEHS. The researchers looked at an inflammatory biomarker called gestational C-reactive protein (CRP) in the Finnish Maternity Cohort, which contains an archive of serum samples collected from approximately 810,000 pregnant women in Finland.

Analysis of serum corresponding to 677 childhood autism cases, and an equal number of matched controls, revealed that the risk of autism among children in the study increased by 43 percent among mothers with CRP levels in the top 20th percentile, and by 80 percent for maternal CRP in the top 10th percentile. These findings could not be explained by maternal age, paternal age, gender, previous births, socioeconomic status, preterm birth, or birth weight. The researchers caution that the results should be viewed in perspective, since the prevalence of inflammation during pregnancy is substantially higher than the prevalence of autism.

*Citation:* [Brown AS, Sourander A, Hinkka-Yli-Salomaki S, McKeague IW, Sundvall J, Surcel HM.](#)  
(<http://www.ncbi.nlm.nih.gov/pubmed/23337946>)

2013. Elevated maternal C-reactive protein and autism in a national birth cohort. *Mol Psychiatry*; doi:10.1038/mp.2012.197 [Online 22 January 2013]. [\[Synopsis\]](#)

### **Cost of mercury pollution**

According to a study supported in part by NIEHS, each year in Europe more than 1.8 million children are born with unsafe prenatal methylmercury exposures. Exposure to methylmercury typically occurs from eating fish, which bioconcentrate the contaminant. Methylmercury affects brain development leading to a lower IQ and, thus, lower earning potential.

To calculate the costs associated with this exposure, the researchers examined mercury concentrations in hair samples from the DEMOCOPHES study of exposure to environmental chemicals, as well as other studies. They assumed that mercury levels below 0.58 micrograms per gram of hair would have little adverse effect. The researchers estimated that preventing exposure within

the European Union would bring an annual benefit equivalent to 600,000 IQ points per year, corresponding to the estimated annual economic benefit of 8-9 billion euro. Prevention would have the most impact in southern Europe, where hair-mercury concentrations were the highest.

*Citation:* Bellanger M, Pichery C, Aerts D, Berglund M, Castano A, Cejchanova M, Crettaz P, Davidson F, Esteban M, Fischer ME, Gurzau AE, Halzlova K, Katsonouri A, Knudsen LE, Kolossa-Gehring M, Koppen G, Ligoeka D, Miklavcic A, Reis MF, Rudnai P, Tratnik JS, Weihe P, Budtz-Jorgensen E, Grandjean P.

(<http://www.ncbi.nlm.nih.gov/pubmed/23289875>)

2013. Economic benefits of methylmercury exposure control in Europe: Monetary value of neurotoxicity prevention. *Environ Health* 12:3. [Synopsis]

### **BPA exposure in the NICU**

A study, supported in part by NIEHS, identified medical devices as a potential source of exposure to bisphenol A (BPA) among premature infants in neonatal intensive care units (NICU). BPA is used to manufacture polycarbonate plastics, which are used in medical devices such as intravenous administration sets, syringes, and catheters.

The researchers examined urinary BPA concentration for 55 infants and categorized each infant's medical device use as low or high, based on the number and invasiveness of devices. They found that the median urinary total BPA concentration of infants who had required four or more medical devices for three previous days was significantly higher, 36.6 micrograms per liter, than for the infants requiring three or fewer devices, 13.9 micrograms per liter. The researchers also collected and analyzed breast milk or formula samples and found that the increased BPA concentration was not associated with the infants' nutritional intake.

*Citation:* Duty SM, Mendonca K, Hauser R, Calafat AM, Ye X, Meeker JD, Ackerman R, Cullinane J, Faller J, Ringer S. 2013. Potential sources of bisphenol A in the neonatal intensive care unit. *Pediatrics* 131(3):483-489. [Synopsis]

### **Global cost of childhood lead exposure**

According to research supported by NIEHS, low-income and middle-income countries experience the largest burden of lead exposure, with cost measured in what are known as international dollars. An international dollar is a hypothetical currency used to compare costs from various countries. It has the same purchasing power as a dollar would have in the U.S.

The researchers calculated lead-associated loss by developing a regression model to estimate average blood lead levels and estimating the lead-attributable economic costs with an environmentally attributable fraction model. They examined only the neurodevelopmental effects of lead, which were assessed using IQ points. The investigators estimate that the total lead-associated economic loss ranges from \$728.6 billion to \$1.1625 trillion international dollars, including \$134.7 billion in Africa, \$142.3 billion in Latin America and the Caribbean, and \$699.9 billion in Asia.

*Citation:* Attina TM, Trasande L.

(<http://www.ncbi.nlm.nih.gov/pubmed/23797342>)

2013. Economic costs of childhood lead exposure in low- and middle-income countries. *Environ Health Perspect* 121(9):1097-1102. [Synopsis]

### **Using membrane transporters to improve crops for sustainable food production**

NIEHS grantees published findings that indicate understanding the biology of plant membrane transporters may be a key contributor to the goal of global food security. With the global population predicted to grow by at least 25 percent by 2050, the need for sustainable production of nutritious foods will be crucial for human and environmental health.

The authors discuss examples where fundamental research is currently being translated into practical applications, such as showing how specialized plant membrane transporters can be used to enhance yields of staple crops, increase nutrient content, and increase resistance to key stresses, including salinity, pathogens, and aluminum toxicity. They also examine potential applications linked to breakthroughs in basic research that are yet to be applied to crop plants.

*Citation:* Schroeder JI, Delhaize E, Frommer WB, Guerinot ML, Harrison MJ, Herrera-Estrella L, Horie T, Kochian LV, Munns R, Nishizawa NK, Tsay YF, Sanders D.

(<http://www.ncbi.nlm.nih.gov/pubmed/23636397>)

2013. Using membrane transporters to improve crops for sustainable food production. *Nature* 497(7447):60-66. [Story]

### **Metabolomics reveals early changes in metabolic pathways for Alzheimer's disease**

With funding from NIEHS, researchers found changes in metabolic pathways that were detectable in blood plasma of Alzheimer's patients. The findings suggest that it might be possible to identify plasma biomarkers for early Alzheimer's disease diagnosis, monitoring disease progression, and evaluating therapeutic approaches.

The researchers used a nontargeted metabolomics approach based on liquid chromatography and mass spectrometry to analyze

cerebrospinal fluid and plasma samples from 45 people in the Mayo Clinic Study on Aging, and Mayo Clinic Alzheimer's Disease Research Center. In total, the investigators found 342 plasma and 351 cerebrospinal fluid significantly altered metabolites. Patients with mild cognitive impairment and Alzheimer's disease showed significant impairment in energy metabolism and other physiological functions. The researchers say that additional research, using targeted metabolomics, could identify specific panels of biomarkers.

*Citation:* [Trushina E, Dutta T, Persson XM, Mielke MM, Petersen RC.](#)

(<http://www.ncbi.nlm.nih.gov/pubmed/23700429>)

2013. Identification of altered metabolic pathways in plasma and CSF in mild cognitive impairment and Alzheimer's disease using metabolomics. PLoS One 8(5):e63644. [[Synopsis](#)]

### **Epigenetic effects of DDT lead to obesity in later generations**

A mouse study, supported in part by NIEHS, indicates that ancestral exposure to the insecticide dichlorodiphenyltrichloroethane (DDT) can promote obesity and associated disease in later generations. The findings imply that environmental exposures experienced several generations ago might influence today's rates of obesity, although the degree of involvement is not known.

The researchers found differential DNA methylation regions, which were epigenetic changes, in sperm of the third generation. Genes associated with these regions were previously shown to be associated with obesity. Although banned in the U.S., DDT is used to control malaria in other parts of the world. The researchers stressed that long-term health and economic effects of DDT exposure on future generations should be considered in areas where DDT is used.

*Citation:* [Skinner MK, Manikkam M, Tracey R, Guerrero-Bosagna C, Haque M, Nilsson EE.](#)

(<http://www.ncbi.nlm.nih.gov/pubmed/24228800>)

2013. Ancestral dichlorodiphenyltrichloroethane (DDT) exposure promotes epigenetic transgenerational inheritance of obesity. BMC Med 11:228. [[Synopsis](#)]

### **Mechanism for amyloid-beta accumulation in Alzheimer's disease**

An NIEHS grantee and his colleagues report that low levels of copper can accumulate in the brain, leading to amyloid-beta plaques that are the hallmark of Alzheimer's disease. The research provides useful information for developing preventative or therapeutic approaches for controlling neurotoxic amyloid-beta levels in the aging brain.

The researchers used normal mice, a mouse model of Alzheimer's disease, and human brain endothelial cells in the study. In normal aging mice, they found that copper accumulated in brain capillaries, which was associated with a reduction in a protein that removes amyloid-beta from the brain called low-density lipoprotein receptor-related protein 1 (LRP1). The same LRP1 decrease appeared in human cells. In the mouse model of Alzheimer's disease, copper accumulated in brain capillaries and the parenchyma, unlike normal aging mice. Overall, this work demonstrated that copper's effect on amyloid-beta homeostasis in the brain depends on whether it accumulates in capillaries or in the parenchyma.

*Citation:* [Singh I, Sagare AP, Coma M, Perlmutter D, Gelein R, Bell RD, Deane RJ, Zhong E, Parisi M, Ciszewski J, Kasper RT, Deane R.](#)

(<http://www.ncbi.nlm.nih.gov/pubmed/23959870>)

2013. Low levels of copper disrupt brain amyloid-beta homeostasis by altering its production and clearance. Proc Natl Acad Sci U S A 110(36):14771-14776. [[Synopsis](#)]

### **DNA methylation in the human genome**

In mammals, 70-80 percent of all cytidine-phosphateguanosine (CpG) dinucleotides are methylated, but NIEHS-supported researchers report that only a fraction of these CpGs likely participate in genome regulation in a developmental context. The DNA methylation signatures, called differentially methylated regions, may be used to guide new, more effective approaches that examine the most informative portion of CpGs.

Genome-wide association studies showed that differentially methylated regions often contained single nucleotide polymorphisms associated with cancer and Alzheimer's disease. The investigators used their set of differentially methylated regions to correctly identify an unknown tissue sample and to classify the types of cells present in a heterogeneous sample.

*Citation:* [Ziller MJ, Gu H, Muller F, Donaghey J, Tsai LT, Kohlbacher O, De Jager PL, Rosen ED, Bennett DA, Bernstein BE, Gnirke A, Meissner A.](#)

(<http://www.ncbi.nlm.nih.gov/pubmed/23925113>)

2013. Charting a dynamic DNA methylation landscape of the human genome. Nature 500(7463):477-481. [[Synopsis](#)]

## Graphene sheets pierce and enter cells

NIEHS grantees report that graphene materials with micrometer-scale dimensions, known as graphene microsheets, can enter cells when their sharp protrusions pierce the cell membrane. Understanding how these graphene sheets interact with cells can help scientists develop materials that are not harmful to the body.

Confocal fluorescence and electron microscopy confirmed that graphene's rough edges and corners could pierce primary human keratinocytes, human lung epithelial cells, and murine macrophages. The imaging also showed that cells could completely internalize graphene sheets with lateral dimensions of 0.5-10 micrometers. More research is needed to understand how the microsheets affect cells, but the researchers say that microsheets might disrupt cytoskeleton and cell motility and cause problems with epithelial barriers.

*Citation:* Li Y, Yuan H, von dem Bussche A, Creighton M, Hurt RH, Kane AB, Gao H.

(<http://www.ncbi.nlm.nih.gov/pubmed/23840061>)

2013. Graphene microsheets enter cells through spontaneous membrane penetration at edge asperities and corner sites. *Proc Natl Acad Sci U S A* 110(30):12295-12300. [[Synopsis](#)]

## Improving health for low-income workers

An NIEHS grantee co-authored a paper that calls for improving the health of low-income workers by integrating health protection and health promotion programs that can be delivered at worksites, state and local health departments, community health centers, and community-based organizations. Low-income workers experience overlapping occupational and nonoccupational risks that can be worsened by limited resources and societal racism.

The authors provide six broad recommendations for reducing health inequities among low-income workers - improve access and quality of work-related data, integrate work environmental factors into care at community health centers, improve the exchange of information and ideas, increase the integration of health and occupational health education and training, test and evaluate new approaches, and improve worker and community engagement.

*Citation:* Baron SL, Beard S, Davis LK, Delp L, Forst L, Kidd-Taylor A, Liebman AK, Linnan L, Punnett L, Welch LS.

(<http://www.ncbi.nlm.nih.gov/pubmed/23532780>)

2013. Promoting integrated approaches to reducing health inequities among low-income workers: applying a social ecological framework. *Am J Ind Med*; doi:10.1002/ajim.22174 [Online 26 March 2013]. [[Synopsis](#)]

## Father's obesity could have epigenetic effects

A study, partially supported by NIEHS, found that newborns with obese fathers had significantly less DNA methylation of the insulin-like growth factor 2 (IGF2) gene. Since reduced DNA methylation of this gene is associated with a higher risk of developing certain cancers, the study findings suggest that a father's obesity could influence his child's future health.

They examined DNA from 79 newborns whose mothers participated in the Newborn Epigenetics Study during pregnancy and also gathered information about both parents using questionnaires and medical records. Even after adjusting for several maternal and newborn characteristics, they observed a persistent inverse association between DNA methylation in the offspring and paternal obesity. The researchers say that the changes in DNA methylation could result from obesity-related factors, such as diet or having diabetes, that were not measured in the study.

*Citation:* Soubry A, Schildkraut JM, Murtha A, Wang F, Huang Z, Bernal A, Kurtzberg J, Jirtle RL, Murphy SK, Hoyo C.

(<http://www.ncbi.nlm.nih.gov/pubmed/23388414>)

2013. Paternal obesity is associated with IGF2 hypomethylation in newborns: results from a Newborn Epigenetics Study (NEST) cohort. *BMC Med* 11:29. [[Synopsis](#)]

## In-house research

### Consequences of ribonucleotide removal by topoisomerase 1

NIEHS researchers, together with collaborators at Umea University in Sweden, have determined that topoisomerase 1 (Top1), an enzyme important for uncoiling DNA during replication and transcription, can also remove ribonucleotides incorporated into DNA during replication.

Using yeast as a model system, the scientists studied strains that were genetically engineered to incorporate a large number of ribonucleotides into DNA, and were defective in RER, Top1, or both. In the absence of RER, Top1 incised the DNA backbone where ribonucleotides were present, thereby initiating the removal of about 5,000 ribonucleotides from the genome. Because the enzymes involved in processing ribonucleotides in DNA are conserved, the authors suggest that the genome instability resulting from Top1 cleavage at ribonucleotides in DNA may be relevant to Aicardi-Goutieres syndrome, and possibly to other autoinflammatory disorders.



Citation: [Williams JS, Smith DJ, Marjavaara L, Lujan SA, Chabes A, Kunkel TA.](#)

(<http://www.ncbi.nlm.nih.gov/pubmed/23375499>)

Topoisomerase 1-mediated removal of ribonucleotides from nascent leading-strand DNA. *Mol Cell* 49(5):1010-1015. [\[Synopsis\]](#)

### **The role of p53 during bacterial pneumonia**

NIEHS researchers recently discovered that the transcription factor p53 modulates host defense through regulating microbicidal function and fate of phagocytes during bacterial pneumonia. This study revealed a fundamental link between defense of genome and host during environmental insult.

The authors used mice that had their p53 genes deleted (p53<sup>-/-</sup>) or in which p53 was pharmacologically inhibited. Both sets of mice displayed enhanced clearance of extracellular bacteria during pneumonia. The lungs of p53<sup>-/-</sup> mice displayed genome-wide induction of NF-kappaB response element-enriched proinflammatory genes in the steady state, and enhanced induction of cytokines upon infection. Despite enhanced bacterial clearance, infected p53<sup>-/-</sup> mice suffered increased mortality from pneumonia, likely due to aggravated lung injury from an overexuberant immune response.

Citation: [Madenspacher JH, Azzam KM, Gowdy KM, Malcolm KC, Nick JA, Dixon D, Aloor JJ, Draper DW, Guardiola JJ, Shatz M, Menendez D, Lowe J, Lu J, Bushel P, Li L, Merrick BA, Resnick MA, Fessler MB.](#)

(<http://www.ncbi.nlm.nih.gov/pubmed/23630228>)

2013. p53 integrates host defense and cell fate during bacterial pneumonia. *J Exp Med* 210(5):891-904. [\[Synopsis\]](#)

### **DNA methylation could predict breast cancer risk**

NIEHS scientists have discovered DNA methylation in blood could prove to be an effective indicator of who will develop breast cancer. Using the NIEHS Sister Study, a nationwide cohort of women, ages 35-74, whose sisters had breast cancer, researchers used DNA extracted from white blood cell samples and assessed methylation at 27,000 sites across the genome.

The team found evidence that women who subsequently develop breast cancer have different blood methylation profiles than women who remain cancer free, and that these methylation differences are detectable months to years before the clinical diagnosis of breast cancer. The scientists also found that epigenetic modifications were significantly more accurate in predicting who will develop breast cancer than the known risk factors and polymorphisms, although they caution their test is not yet accurate enough for clinical use.

Citation: [Xu Z, Bolick SC, DeRoo LA, Weinberg CR, Sandler DP, Taylor JA.](#)

(<http://www.ncbi.nlm.nih.gov/pubmed/23578854>)

2013. Epigenome-wide association study of breast cancer using prospectively collected Sister Study samples. *J Natl Cancer Inst* 105(10):694-700. [\[Synopsis\]](#) [\[Story\]](#)

### **Observing a DNA polymerase using time-resolved crystallography**

NIEHS scientists utilized a technique called time-resolved crystallography to examine how a model human DNA polymerase beta (pol beta) chooses a nucleotide during DNA synthesis. The technique confirmed features of the computational results the researchers had generated earlier, but also revealed pol beta changes its shape, depending on whether it incorporates a complementary base pair or correct nucleotide.

The study also found that pol beta forms a third metal binding site during correct, but not incorrect, nucleotide insertion, and that pyrophosphate more easily dissociates after incorrect nucleotide insertion. Prior to this evidence, researchers believed that only two metal ion binding sites were used by all polymerases in their mechanism of action and pyrophosphate was released instantly. The researchers hope this information will lead to a better understanding of the potential causes of disease.

Citation: [Freudenthal BD, Beard WA, Shock DD, Wilson SH.](#)

(<http://www.ncbi.nlm.nih.gov/pubmed/23827680>)

2013. Observing a DNA polymerase choose right from wrong. *Cell* 154(1):157-168. [\[Synopsis\]](#) [\[Story\]](#)

### **Early mouse development influences norepinephrine neuron diversity**

Applying a technique known as intersectional genetic fate mapping to the developing mouse brain, NIEHS researchers characterized neurons that produce and release norepinephrine (NE), a hormone and neurotransmitter. As a result, they were the first to develop a map of communication pathways in the growing mouse brain. Since NE neurons are involved in several physiological processes, such as food intake and sleep, and are lost in Parkinson's and Alzheimer's diseases, understanding NE neurons will lead to improvements in human health.

The scientists found that NE neurons derived from a specific rhombomere, or segment in the developing hindbrain, shared common features in the adult brain. The group also determined that these various subgroups of NE neurons were talking to many different parts of the adult mouse brain. Prior to this study, neuroscientists believed only one group of NE neurons

communicated with the cerebral cortex.

*Citation:* [Robertson SD, Plummer NW, de Marchena J, Jensen P.](#)

(<http://www.ncbi.nlm.nih.gov/pubmed/23852112>)

2013. Developmental origins of central norepinephrine neuron diversity. *Nat Neurosci* 16(8):1016-1023. [[Synopsis](#)] [[Story](#)]

### **APOBEC cytidine deaminases generate many mutations in human cancers**

NIEHS researchers and colleagues at the Broad Institute of MIT and Harvard in Cambridge, Mass., report that a set of proteins, known to protect against retroviruses and retrotransposons, can cause mutations that are widespread in human cancers.

These mutations, which have a characteristic mutation signature, are produced by apolipoprotein B mRNA-editing enzyme, catalytic polypeptide-like (APOBEC) cytidine deaminases. Scientists from the team developed an analysis to detect and statistically evaluate the prevalence of APOBEC mutations in 2,680 tumor samples, collected from 14 types of cancer. Using this strategy, they discovered that APOBEC enzymes produce the majority of mutations in some bladder, cervical, breast, head and neck, and lung tumors. They also found APOBEC signature mutations specifically in genes that have been implicated in cancer development and progression, highlighting a potential link between APOBEC enzymes and carcinogenesis.

*Citation:* [Roberts SA, Lawrence MS, Klimczak LJ, Grimm SA, Fargo D, Stojanov P, Kiezun A, Kryukov GV, Carter SL, Saksena G, Harris S, Shah RR, Resnick MA, Getz G, Gordenin DA.](#)

(<http://www.ncbi.nlm.nih.gov/pubmed/23852170>)

2013. An APOBEC cytidine deaminase mutagenesis pattern is widespread in human cancers. *Nat Genet* 45(9):970-976.

[[Synopsis](#)] [[Story](#)]

### **Tanning gene linked to increased risk of testicular cancer**

Collaborative efforts between NIEHS and the University of Oxford have found that a variant in a gene that promotes skin tanning is associated with an increased risk of testicular cancer. This variant, also known as a single-nucleotide polymorphism (SNP), is located in the KITLG gene, a gene that is controlled by the tumor suppressor p53, the most commonly mutated gene in human cancers.

The SNP confers protection to the skin against sun damage, by increasing production of pigmented cells called melanocytes. The authors suggest that during human evolution, this SNP has become more common in populations with light skin for this beneficial reason. However, in testicular cells, the situation appears reversed. The researchers hypothesize that increased cell division driven by the KITLG SNP may permit the growth of tumor cells, increasing cancer risk for those that carry the gene variant.

*Citation:* [Zeron-Medina J, Wang X, Repapi E, Campbell MR, Su D, Castro-Giner F, Davies B, Peterse EF, Sacilotto N, Walker GJ, Terzian T, Tomlinson IP, Box NF, Meinshausen N, De Val S, Bell DA, Bond GL.](#)

(<http://www.ncbi.nlm.nih.gov/pubmed/24120139>)

2013. A polymorphic p53 response element in KIT ligand influences cancer risk and has undergone natural selection. *Cell*

155(2):410-422. [[Synopsis](#)] [[Story](#)]

### **Assessing cockroach allergen exposure via its structure**

NIEHS scientists and their collaborators have obtained the crystal structure of the cockroach allergen Bla g 1. It is the first structure to be solved for this group of insect proteins. Determining the structure of Bla g 1 allows for the standardization of assays that measure it in absolute units.

The X-ray crystallography revealed that Bla g 1 had a novel fold with the capacity to bind various lipids. Further analysis using mass spectrometry and nuclear magnetic resonance indicated that Bla g 1 could accommodate a variety of hydrophobic ligands that could be important for a variety of physiological purposes, including sensitizing humans. Overall, the authors believe that this work would allow a better assessment of Bla g 1 exposure, which is important in evaluating new intervention strategies. Additionally, the structure may be useful in designing new immunotherapies.

*Citation:* [Mueller GA, Pedersen LC, Lih FB, Glesner J, Moon AF, Chapman MD, Tomer KB, London RE, Pomes A.](#)

(<http://www.ncbi.nlm.nih.gov/pubmed/23915714>)

2013. The novel structure of the cockroach allergen Bla g 1 has implications for allergenicity and exposure assessment. *J Allergy Clin Immunol* 132(6):1420-1426. [[Synopsis](#)]

### **Probiotics use during pregnancy may reduce diseases in children**

Based on data from the Norwegian Mother and Child Cohort Study (MoBa), a research team led by NIEHS scientists have determined that, for the general population, probiotics consumed during pregnancy and infancy may help prevent atopic eczema and rhinoconjunctivitis in early childhood.

The researchers used data from more than 40,000 mother and children pairs participating in the MoBa study, which recruited Norwegian women between 1999 and 2008. Thirty-seven percent of pregnant mothers in the study consumed these probiotic milk and yogurt products, and 18 percent of them also gave their child probiotic milk products after 6 months of age. The researchers found that maternal probiotic milk consumption in pregnancy, as well as consumption during early childhood, was associated with a slightly reduced relative risk of atopic eczema at 6 months, and rhinoconjunctivitis symptoms between 18-36 months.

*Citation:* Bertelsen RJ, Brantsaeter AL, Magnus MC, Haugen M, Myhre R, Jacobsson B, Longnecker MP, Meltzer HM, London SJ.

(<http://www.ncbi.nlm.nih.gov/pubmed/24034345>)

2013. Probiotic milk consumption in pregnancy and infancy and subsequent childhood allergic diseases. *J Allergy Clin Immunol*; doi:10.1016/j.jaci.2013.07.032 [Online 10 September 2013]. [[Synopsis](#)]

### **Identification of novel immune regulatory elements and epigenetic plasticity in memory lymphocytes**

A collaborative team, led by NIEHS investigators, determined that the global reprogramming of the epigenome, or the epigenetic modifications of DNA, permits adult somatic cells to differentiate into diverse cell types.

To investigate the function of DNA methylation changes associated with immune activation, the authors determined whether activation-induced differentially methylated regions were enriched for regulatory elements and also found that Alu elements display differential methylation patterns, correlated with decreased expression of the de novo methyltransferase DNMT3A in GC B cells. The authors propose that the loss of DNA methylation during the naive to GC B cell transition permits these cells to differentiate toward memory or plasma cell fates, and to generate the differential response to antigenic challenge.

*Citation:* Lai AY, Mav D, Shah R, Grimm SA, Phadke D, Hatzi K, Melnick A, Geigerman C, Sobol SE, Jaye DL, Wade PA.

(<http://www.ncbi.nlm.nih.gov/pubmed/24013550>)

2013. DNA methylation profiling in human B cells reveals immune regulatory elements and epigenetic plasticity at Alu elements during B-cell activation. *Genome Res* 23(12):2030-2041. [[Synopsis](#)]

## **National Toxicology Program research**

### **Spontaneous mesotheliomas in F344/N rats are characterized by dysregulation of cellular growth and immune function pathways**

Scientists wanted to understand why aged male Fischer 344/N rats are prone to developing spontaneous peritoneal mesotheliomas that arise predominantly from the tunica vaginalis of the testes.

Global gene expression profiles of spontaneous mesotheliomas from these rats were taken from 2-year National Toxicology Program (NTP) carcinogenicity bioassays. The analyses determined that these tumors were associated with upregulation of various growth factors, oncogenes, cytokines, pattern recognition response receptors, and pathogen-associated molecular patterns receptors, and the production of reactive oxygen and nitrogen species, as well as downregulation of apoptosis pathways. Alterations in these pathways, in turn, trigger molecular responses that stimulate cell proliferation and promote tumor survival and progression.

*Citation:* Blackshear PE, Pandiri AR, Ton TV, Clayton NP, Shockley KR, Peddada SD, Gerrish KE, Sills RC, Hoenerhoff MJ.

(<http://www.ncbi.nlm.nih.gov/pubmed/23980201>)

2013. Spontaneous mesotheliomas in F344/N rats are characterized by dysregulation of cellular growth and immune function pathways. *Toxicol Pathol*; doi:10.1177/0192623313501894 [Online 26 August 2013].

### **Chronic exposure of renal stem cells to inorganic arsenic induces a cancer phenotype**

Evidence indicated that developmental arsenic exposure impacts renal carcinogenesis in humans and mice, and since emerging theory suggested cancer may be a disease of stem cells (SCs), the researchers wanted to see if inorganic arsenic targets SCs, or partially differentiated progenitor cells (PCs), for oncogenic transformation.

Scientists chronically exposed the rat kidney SC/PC cell line, RIMM-18, to low-level arsenite (500 nM) for up to 28 weeks, and found that dysregulation of SC maintenance genes and signaling pathways are common during oncogenesis. During arsenite exposure, expression of several genes associated with normal kidney development and SC regulation and differentiation, such as Wt-1, Wnt-4, and Bmp-7 were aberrantly altered. These data reveal that multipotent SCs may be targets of arsenic during renal carcinogenesis.

*Citation:* Tokar EJ, Person RJ, Sun Y, Perantoni A, Waalkes MP.

(<http://www.ncbi.nlm.nih.gov/pubmed/23137061>)

2013. Chronic exposure of renal stem cells to inorganic arsenic induces a cancer phenotype. *Chem Res Toxicol* 26(1):96-105.



## **RNASeq profiling reveals novel hepatic gene expression pattern in aflatoxin B1 treated rats**

Researchers used deep sequencing (DESeq) to investigate the subchronic effects of 1 ppm aflatoxin B1 (AFB1), a potent hepatocarcinogen, on the male rat liver transcriptome prior to onset of histopathological lesions or tumors.

DESeq analysis identified 1,026 differentially expressed transcripts at greater than two-fold change compared to 626 transcripts by microarray due to base pair resolution of transcripts by RNA-Seq, probe placement within transcripts or an absence of probes to detect novel transcripts, splice variants and exons. They found that the rat transcriptome contains many previously unidentified, AFB1-responsive exons and transcripts supporting RNA-Seq's capabilities to provide new insights into AFB1-mediated gene expression leading to hepatocellular carcinoma.

*Citation:* [Merrick BA, Phadke DP, Auerbach SS, May D, Stiegelmeier SM, Shah RR, Tice RR.](#)

*(<http://www.ncbi.nlm.nih.gov/pubmed/23630614>)*

2013. RNA-Seq profiling reveals novel hepatic gene expression pattern in aflatoxin B1 treated rats. PLoS One 8(4):e61768.

## **Recruitment of normal stem cells to an oncogenic phenotype by noncontiguous carcinogen-transformed epithelia depends on the transforming carcinogen**

NTP scientists wanted to know whether the recruitment of normal stem cell (NSCs) into cancer stem cells (CSCs) by noncontact co-culture was specific to arsenic-transformed isogenic malignant epithelial cells (MECs). Therefore, they utilized co-culture to examine the effects of neighboring noncontiguous cadmium-transformed MECs (Cd-MECs) and N-methyl-N-nitrosourea-transformed MECs (MNU-MECs) on NSCs.

They found that Cd-MECs can recruit nearby NSCs into a CSC-like phenotype, but MNU-MECs do not. Thus, the recruitment of NSCs into CSCs by nearby MECs is dependent on the carcinogen originally used to malignantly transform the MECs.

*Citation:* [Xu Y, Tokar EJ, Person RJ, Orihuela RG, Ngilame NN, Waalkes MP.](#)

*(<http://www.ncbi.nlm.nih.gov/pubmed/23687063>)*

2013. Recruitment of normal stem cells to an oncogenic phenotype by noncontiguous carcinogen-transformed epithelia depends on the transforming carcinogen. Environ Health Perspect 121(8):944-950.

## **Bisphenol A affects androgen receptor function via multiple mechanisms**

BPA is an endocrine disrupting compound that affects the development and function of the female and male reproductive system. Since its mechanism of action is unclear, the research team initiated the study to investigate how BPA may affect ten different nuclear receptors.

The scientists examined stable cell lines that contained an individual nuclear receptor ligand binding domain-linked to the beta-Gal reporter using a quantitative high throughput screening format in the Tox21 screening program. The results showed that two receptors, estrogen receptor alpha (ERalpha) and androgen receptor (AR), are affected by BPA in opposite direction. The team also performed transient transfection experiments with full-length receptors and their corresponding response elements linked to luciferase reporters, as well as evaluating BPA effects in nuclear translocation assays using EGFP-tagged receptors. The authors found that BPA enhanced ERalpha nuclear foci formation, but at a 100-fold higher concentration. BPA was unable to activate AR.

*Citation:* [Teng C, Goodwin B, Shockley K, Xia M, Huang R, Norris J, Merrick BA, Jetten AM, Austin CP, Tice RR.](#)

*(<http://www.ncbi.nlm.nih.gov/pubmed/23562765>)*

2013. BisphenolA affects androgen receptor function via multiple mechanisms. Chem Biol Interact 203(3):556-564.

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NTP research summaries were contributed by NTP staff and submitted by their branch chiefs.

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